PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JAB 1715-PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/04368	International filing date *(day/month/year)* 24.04.2003	Priority date *(day/month/year)* 03.05.2002
International Patent Classification (IPC) or both national classification and IPC C08G63/06		
Applicant JANSSEN PHARMACEUTICA N.V. et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16.10.2003	26.07.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Zeslawski, W Telephone No. +49 89 2399-7159

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

Werner Van Borm
29 -07- 2004
5476

To:

QUAGHEBEUR Luc
JANSSEN PHARMACEUTICA N.V.
Turnhoutseweg 30
B-2340 Beerse
BELGIQUE

RECEIVED
28 JUL 2004
Patent department

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Applicant's or agent's file reference JAB 1715-PCT	Date of mailing *(day/month/year)* 26.07.2004
	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/04368	24.04.2003	03.05.2002

Applicant
JANSSEN PHARMACEUTICA N.V. et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Borinski, W Tel. +49 89 2399-8237

Form PCT/IPEA/416 (January 2004)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/04368

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-37 as originally filed

Claims, Numbers

1-26 filed with telefax on 06.07.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-26
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-26
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-26
	No:	Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following documents:

D1: WO 02 38184 A
D2: US-B1-6 322 805
D3: US-B1-6 211 249
D4: WO 98 35631 A
D5: US-A-4 716 203
D6: EP-A-0 258 780
D7: EP-A-0 258 749
D8: WO 97 45105 A

Concerning Point V:

Novelty (Art.33(2) PCT)

Document D1 discloses diblock co-polymer of formula BA, wherein A is polylactide-co-glycolide and B is selected from a group of hydrophilic polymers (p.4 l.14-33). The B block of the copolymer has M_w in between 500 and 10000 Da (p.5 l.12-14).

Document D2 discloses a polymer of formula: R_1-(-OCH_2CH_2-)$_m$-X, wherein: R1 can be hydrogen; m is larger then 2, preferably from 20-75; and X is hydrophobic biodegradable segment, e.g. poly(lactic-co-glycolic acid). The polyethylene oxide segment has M_w larger then 88 (for m=2), preferably from 880-3200 ($20 < m < 75$) (col.4 l.39-55).

Document D3 disclose a polymeric composition comprising diisocyanate coupled AB diblocks, where A is a polyester unit derived from e.g. glycolic acid, β-propiolactone, ε-caprolactone, δ-valerolactone, trimethylene carbonate, γ-butyrolactone, and B is obtained by reacting a polyalkylene oxide end-capped with a non-reactive group, said AB diblock being **further** diisocyanate coupled to produce di-diblock polymers (claim 1). Moreover, the B block can vary in size from 100 up to 200000 Da (col.33 l.33-64).

Each of the documents D4-D8 discloses a pharmaceutically acceptable diblock polymer of formula A-B, wherein the polymer block A represents a linear hydrophilic polymer and the block B represents a biodegradable polymer (**D4**: examples 10-14 p.37-39; **D5**: example 31; **D6**: example 27; **D7**: example 31; **D8**: example 16).

Inventive Step (Art.33(3) PCT)

Document D2 appears to represent the prior art reference which shares the most technical features with the subject matter of the present application. The subject matter of claim 1 is distinguished from the closest prior art document by the composition of the

polymer block B, which comprising at least two different monomers selected from glycolic acid, propiolactone, γ-butyrolactone, δ-valerolactone, γ-valerolactone, ε-caprolactone, trimethylene carbonate, p-dioxanone, tetramethylene carbonate, ε-lactone and 1,5-dioxepan-2-one. Furthermore, the polymer block A has a restricted molecular weight, < 1000.

The technical effect corresponding to these distinguishing features appears to be an improvement in drugs incorporation into micelles of the polymer. Consequently, the objective technical problem over closest prior art document D2 is the provision of a diblock polymer of formula A-B, which can incorporate drugs in aqueous solution without the need of complex incorporation techniques such as e.g the use of organic solvents, followed by their evaporation, or the use of dialysis.

There is, however, neither in D2, nor in any other prior art document, if taken separately or in combination, any teaching or suggestion which points into the direction of the combination of features according to the claimed in the present application. Therefore, the subject matter of the present application appears to be based on an inventive step.

Claims

1 A diblock copolymer of formula A-B wherein
polymer block A represents a linear pharmaceutically acceptable hydrophilic polymer with a molecular weight < 1,000, and
polymer block B represents a polymer comprising at least two different monomers selected from glycolic acid, propiolactone, γ-butyrolactone, δ-valerolactone, γ-valerolactone, ε-caprolactone, trimethylene carbonate, p-dioxanone, tetramethylene carbonate, ε-lactone, 1,5-dioxepan-2-one characterized in that the diblock copolymer is liquid at a temperature below 50°C.

2 A diblock copolymer according to claim 1 wherein polymer block B represents a polymer comprising monomers selected from glycolic acid, propiolactone, γ-butyrolactone, δ-valerolactone, ε-caprolactone, trimethylene carbonate, p-dioxanone, tetramethylene carbonate, ε-lactone, 1,5-dioxepan-2-one or mixtures thereof.

3. A diblock copolymer according to claim 1 wherein polymer block B represents a polymer comprising monomers of trimethylene carbonate and monomers selected from glycolic acid, propiolactone, γ-butyrolactone, δ-valerolactone, γ-valerolactone, ε-caprolactone, p-dioxanone, tetramethylene carbonate, ε-lactone, 1,5-dioxepan-2-one or mixtures thereof.

4. A diblock copolymer according to claim 3 wherein polymer block B represents a polymer comprising monomers of trimethylene carbonate and monomers selected from glycolic acid, propiolactone, γ-butyrolactone, δ-valerolactone, ε-caprolactone, p-dioxanone, tetramethylene carbonate, ε-lactone, 1,5-dioxepan-2-one or mixtures thereof.

5. A diblock copolymer according to claim 1 wherein polymer block B represents a polymer comprising monomers selected from propiolactone, γ-butyrolactone, δ-valerolactone, γ-valerolactone, ε-caprolactone, trimethylene carbonate, p-dioxanone, tetramethylene carbonate, ε-lactone, 1,5-dioxepan-2-one.

6. A diblock copolymer according to claim 5 wherein polymer block B comprises two different monomers selected from propiolactone, γ-butyrolactone, δ-valerolactone, γ-valerolactone, ε-caprolactone, trimethylene carbonate,

p-dioxanone, tetramethylene carbonate, ε-lactone, 1,5-dioxepan-2-one.

7. A diblock copolymer according to claim 6 wherein polymer block B comprises monomers selected from ε-caprolactone and trimethylene carbonate.

8. A diblock copolymer according to any one of claims 1 to 7 wherein polymer block A represents poly(C_{1-20}alkylene oxide) or a derivative thereof.

9. A diblock copolymer according to claim 8 wherein the poly(C_{1-20}alkylene oxide) or the derivative thereof is poly(ethylene glycol) or a derivative thereof, in particular poly(ethylene glycol) monomethylether.

10. A diblock copolymer according to claim 9 wherein the poly(ethylene glycol) or a derivative thereof has a molecular weight ranging from > 350 to ≤ 750.

11. A diblock copolymer according to claim 10 wherein the poly(ethylene glycol) or the derivative thereof has a molecular weight of 750.

12. A diblock copolymer according to any one of claims 1 to 11 having a molecular weight ranging from 2,000 to 10,000.

13. A diblock copolymer according to claim 12 having a molecular weight ranging from 2,000 to 8,000.

14. A diblock copolymer according to claim 13 having a molecular weight ranging from 2,500 to 7,000.

15. A diblock copolymer according to any one of claims 1 to 14 being a liquid at room temperature or at 37°C.

16. A composition comprising an active ingredient and one or more diblock copolymers of formula A-B according to any one of claims 1 to 15 characterized in that the composition is liquid below 50°C.

17. A composition according to claim 16 wherein the composition is non-aqueous.

18. A pharmaceutical dosage form comprising a therapeutically effective amount of a

composition according to claim 16 or 17.

19. A pharmaceutical dosage form according to claim 18 characterized in that the dosage form is suitable for oral administration.

20. A pharmaceutical dosage form according to claim 18 characterized in that the dosage form is suitable for parenteral administration.

21. A pharmaceutical dosage form according to any one of claims 18 to 20 wherein the dosage form is an aqueous solution.

22. A process to prepare an aqueous solution comprising an active ingredient and one or more diblock copolymers of formula A-B according to any one of claims 1 to 15 characterized by mixing the active ingredient with the one or more liquid copolymers, i.e. at a temperature below 50°C, followed by addition of water while stirring.

23. A process to prepare an aqueous solution comprising an active ingredient and one or more diblock copolymers of formula A-B according to any one of claims 1 to 15 characterized by
a) mixing the one or more copolymers with water at a temperature below 50°C, followed by
b) the addition of the active ingredient to the aqueous polymeric solution obtained under a) while stirring.

24. Use of a composition according to claim 16 or 17 for the manufacture of a pharmaceutical dosage form for oral administration to a human or non-human animal in need of treatment.

25. Use of a composition according to claim 16 or 17 for the manufacture of a pharmaceutical dosage form for parenteral administration to a human or non-human animal in need of treatment.

26. A pharmaceutical package suitable for commercial sale comprising a container, a pharmaceutical dosage form according to any one of claims 18 to 21, and associated with said package written matter.